Remarks

Claim 1 has been amended to further define characteristics of the compounds which modulate beta 1 integrin function by defining the epitope present on beta 1 integrin to which the modulator compound must bind. Support may be found at page 24, lines 19 to 24 and at page 25, lines 15 to 18 of the application. Claim 1 has been further amended to more specifically define, in functional terms, the modulation which occurs following the binding of beta 1 by the modulator compounds at the epitope defined in amended Claim 1. In particular, the subject matter of former Claims 2 and 3 have been introduced into Claim 1. Support for "an increase in the anabolism of the extracellular matrix" can be found at page 47, line 17 and page 61, line 19 of the application.

In view of the amendment made to Claim 1, Claims 2 and 3 have been cancelled.

New Claim 19 states that the modulator compound can be a synthetic peptide. Support may be found in the description on page 25, line 22 and further on page 48, lines 24.

New Claim 20 is supported in the description on page 25, line 28 through to page 29, line 2 and further on page 48, lines 23 to 24.

New Claim 21 is supported in the description on page 26, lines 4 to 8 and further on page 28, line 2 through to page 31, line 22 and further on page 48, lines 23 to 26 of the description.

New Claim 22 is supported in the description on page 23, line 24 and further at lines 27 to 28.

New Claim 23 is supported in the description on page 48, line 5, figure 9 and page 60, line 5 with respect to an increase in inactive MMP9, while a decrease in MMP1 is supported in the specification on page 48, line 6 and page 61, line 29.

New Claim 24 is supported in the description on page 48, line 5 and further on page 61, line 28.

New Claim 25 is supported in the description on page 48, line 15 to 26.

New Claim 26 is supported in the description on page 62, lines 2 to 19 and further in the examples on page 55, line 24 onwards.

New Claim 27 is based on the description on page 20, lies 13 and 14 which indicates that emphysema is a condition present in COPD, hence the treatment of emphysema will treat COPD.

35 U.S.C. 112

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. In particular, the rejection states that the use of "JB1a" as the sole means of identifying the claims antibody and hybridoma renders the claim indefinite as JB1a is considered merely to be a laboratory designation, which does not clearly define the claimed product.

The Applicants respectfully submits that this is in error. The JB1a nomenclature describes the antibody by the proprietor of the antibody, Chemicon International. The rejection is correct that the JB1A antibody was previously designated J10. However, it is clear that, at the time of the filing date of this application, the name used to describe the clone and associated antibody was JB1A. To support this assertion, the Applicants submit a print-out of the Chemicon International website order page from September 23, 2002 which shows that the antibody is known as JB1A, and that it was *formerly* known as J10. Hence, the J10 nomenclature no longer applies and did not apply at that time. The Applicants *correctly* identified the antibody with respect to the name associated with it, at the time of filing.

Furthermore, the Applicants further submit a photocopy of a page of the Chemicon International catalogue which is marked "© 2001 – CHEMICON International, Inc." this being the "Datasheet" referred to in the foregoing website page provided above, which further shows that at the time of filing of this application, the commercial clone, as recited in Claim 16, was known as JB1A. Hence, the commercial clone is only defined by a sole name. The JB1A nomenclature *replaced* the J10 nomenclature – it is *not* an alternative. One skilled in the art would therefore only refer to the antibody as JB1A. Hence, the Applicants respectfully submit that the JB1A nomenclature is not merely a laboratory designation and is in compliance with §112.

Claim 16 is further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the rejection recites that the hybridoma which produces the JB1a antibody, as a required element, must be known and readily available to the public. The rejection states that the Office will only accept commercial availability as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has access to the material.

The Applicants provide three documents which factually demonstrate that the JB1a clone was commercially available from Chemicon, as described in this application, and that this availability was at a price and under conditions of supply which allowed any third party to access the material. First, a print-out of the Chemicon International website, dated September 23, 2002 is provided. This evidences that the JB1a clone was available to the public from the Chemicon International website as of that date. Also attached is a datasheet pertaining to the JB1a clone.

This further confirms the characteristics of the JB1a clone and, in particular, that it is appropriate for use in the claimed subject matter.

Further provided is a copy of selected extracts of the supply catalogue of Chemicon, dated 2004. It can be seen on the extract of page 198 of this catalogue that there is a clear entry pertaining to the "Intergrin β1 [CD29], a.a. 82-87, clone JB1A (originally designated J10), in the second from the last row. It is further shown that the price of the vial is GBP £219. The Applicants submit that both of these sources, i.e., the Chemicon website and the Chemicon catalogue, clearly and factually demonstrate that the JB1a clone, as referred to in this specification was widely available to third parties and was available at a price which would be seen as unremarkable by one skilled in the art. The skilled practitioner, having read this specification, would fully expect, based on the teachings of the description, for example on page 26, lines 6 to 8 and page 51, line 5, that the JB1a clone could be obtained from Chemicon, and it would have been fully within the scope of the abilities of one skilled in the art to refer to the Chemicon product catalogue or website to obtain the indicated products.

The Applicants therefore respectfully submit that the JB1a clone *was* readily available to the public at the filing date of this application. Reconsideration and withdrawal of the Section 112, first paragraph rejection is respectfully requested.

Written description

Claims 1-4 and 15-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, on the grounds that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed.

The rejection indicates that the Applicants are considered to be in possession of a method of promoting tissue repair in lung emphysema using an antibody derived from the JB1a clone. However, the rejection states that the Applicants are not considered to be in possession of a method of promoting *any* tissue repair using *any* compound which modulates the function of beta 1 integrin (Claim 1), metalloproteinase (MMP) balance (Claim 2), or apoptosis (Claim 3).

The description on page 48, lines 15 to 22, in summarizing the findings of experimentation conducted by the Applicants, using a modulator or beta 1 integrin, which results in a reduction of cell death (apoptosis), suggest a common mode of action which can be applicable to a wide variety of disease conditions where the extracellular matrix is degraded and cannot be replenished. In particular, the description teaches "The potential of these findings lie in tissue repair in disease where the matrix is degraded and cannot be replenished as in diseases that include but not exclusive to COPD. The finding may offer a venue for therapeutic intervention in diseases where the only current lines for therapy focus on alleviating the symptoms by the use of anti-inflammatory agents but has no potential for regaining function. This could be achieved via the administration of humanised, chimeric or human antibodies or synthetic peptides or chemicals capable of binding beta1 integrin and inhibiting cell death". The specification continues "In summary, the results herein address a different potential therapeutic modality which focuses on increasing cell viability and ECM anabolism instead of decreasing catabolism".

Accordingly, the Applicants have described a novel approach, which although exemplified in relation to the treatment of emphysema in the lung (one aspect of COPD), the Applicants identified the effects mediated by the beta 1 integrin modulator compound, in particular, inhibition of apoptosis and promotion of ECM (extracellular matrix) anabolism, result

in a novel approach to the treatment of conditions not solely limited to emphysema, but also extending to other conditions where the extracellular matrix is degraded. Central to the ability to apply the approach identified by the Applicants of using modulation of beta 1 integrin as identified by the Applicants for the promotion of tissue repair, is the fact that beta 1 integrin modulation of the type described in this application, is shown to increase cell viability and extracellular matrix anabolism, rather than decreasing catabolism. That is the modulation of beta 1 integrin actively enhances extracellular matrix anabolism rather than merely slowing down its breakdown.

Reconsideration and withdrawal of the Section 112, first paragraph rejection is respectfully requested.

Enablement

Claims 1-4 and 15-16 are rejected under 35 U.S.C. 112, first paragraph on the grounds that the specification, while being enabling for a method of promoting tissue repair in lung emphysema comprising administering the monoclonal antibody produced by commercial clone JB1a, does not reasonably provide enablement for a method of promoting any "tissue repair" comprising the step of administering any "compound which modulates the function of beta 1 integrin" to a tissue in need of repair. In particular, the rejection recites that the teachings of this specification do not enable one skilled in the art to practice the claimed subject matter without undue experimentation.

The Applicants respectfully submit that amended Claim 1, in identifying the epitope to which the modulator compounds must bind, provides a clear teaching, which would be understood by one skilled in the art, as how to use the claimed subject matter. The Applicants submit that, in defining the epitope to which the beta 1 modulator compounds must bind to

mediate the desired modulatory effect, the Applicants provided sufficient structural information to enable one skilled in the art to make and use the compound, as claimed.

Furthermore, the Applicants respectfully submit that the assertion in the rejection on page 6 of the Office Action that the "specification fails to demonstrate the effect of the claimed compounds on tissue repair" is in error. The Applicants draw the attention of the Examiner to the examples and, in particular, to the results shown in Figures 28 and 29, as described on page 45 of the instant specification which show improved histology and accordingly associated tissue repair in cells obtained from an in-vivo mouse model. A number of the other examples, in particular the results shown in Figures 17 to 27 provide further identification of improved tissue function, following treatment with the JB1a antibody.

As discussed by the Applicants on page 48, lines 15 through 22, the examples provide a clear basis for one skilled in the art to extrapolate the methodology exemplified in this specification to other disease conditions where degradation of the extracellular matrix occurs. Further, this specification makes it clear that such a therapeutic approach would be highly desirable to one skilled in the art, based on the fact that the typical therapeutic intervention for such diseases related to the administration of anti-inflammatory agents. As indentified by the Applicants in the specification, such anti-inflammatory agents would not function to regain tissue function.

Reconsideration and withdrawal of the Section 112, first paragraph rejection is respectfully requested.

Response to rejections under 35 U.S.C. 102(b)

Claims 1-4 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Leu. The rejection recites that Leu teaches a method of promoting tissue repair comprising contacting CCN 1 which modulates the function of beta 1 integrin in angiogenesis.

The Applicants respectfully submit that Leu does not anticipate Claim 1 as amended. In particular, Leu uses the anti-beta 1 antibody derived from clone P4C10. This monoclonal antibody binds to beta 1 integrin at a binding epitope comprising residues 207-218. This epitope is, therefore, different from the binding epitope defined in Claim 1 and as bound by the Applicants' beta 1 integrin modulator compounds. In this specification, on page 46, line 21 through to page 47, line 7, it is specifically discussed that the domain of beta 1 integrin to which the modulatory compounds bind to mediate their effect, is different to the domain which comprises the amino acid residues 207-218. Leu does not disclose a binding epitope which includes the binding epitope identified by the Applicants. Furthermore, the functional effect which is mediated by the beta 1 antibody disclosed in Leu is functionally distinct to that achieved by the Applicants' beta 1 integrin modulation.

Further, the Applicants respectfully submit that angiogenesis and tissue repair are not synonymous. Angiogenesis is accompanied by cell proliferation, whereas the Applicants' modulate tissue repair by binding a modulator compound to beta 1 integrin at an epitope comprising amino acid residues 82-87. This binding, in turn, mediates a number of effects, such as the reduction in apoptosis, with the focus of this being epithelial-mesenchymal populations. The beta 1 integrin modulation observed in this application did not increase cell proliferation.

With regard to comments in the rejection that "While the prior art teachings may be silent as to the peptide/antibody "modulates the MMP balance", "modulates apoptosis" "wherein the

modulation of apoptotic activity has a resultant modulation in the MMP balance" per se; the method, the product used in the reference method are the same as the claimed method. Therefore, these claimed limitations are considered inherent properties of the referenced compounds". The Applicants respectfully disagree. It is incorrect to extrapolate that just because 2 groups of compounds bind to the same target ligand that they mediate the same end effect. This is particularly the case when the compounds of the prior art and the claimed compounds are compared, as they in fact bind to different epitopes of beta-1 integrin. In the specific case of antibodies binding to different target epitopes on the same ligand, it cannot be simply concluded that two antibodies will mediate the same downstream effect on a ligand purely because they have binding specificity for it. Those skilled in the art are well versed in the principles of antibody binding and are fully cognisant of the fact that antibodies binding to different epitopes on the same ligand, can not be assumed to mediate identical effector functions. Hence, the Applicants disagree with the assertion that the beta 1 integrin binding compounds of Lin et al. would mediate the effects disclosed in the solicited claims simply because the P4C10 antibody binds to beta 1 integrin.

The Applicants therefore respectfully submit that Leu does not anticipate the claimed subject matter. Withdrawal of the rejection is respectfully requested.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin. The rejection states that Lin teaches CCN3 induces neovascularisation when implanted in rat cornea.

The Applicants respectfully submit that Leu does not anticipate Claim 1 as amended. In particular, Lin uses the anti-beta 1 antibody derived from clone P4C10. This monoclonal antibody binds to beta 1 integrin at a binding epitope comprising residues 207-218. This epitope is therefore different from the binding epitope defined in Claim 1 and as bound by the beta 1

integrin modulator compounds. In this specification, on page 46, line 21 through to page 47, line 7, it is specifically discussed that the domain of beta 1 integrin to which the modulatory compounds bind to mediate their effect, is different from the domain which comprises the amino acid residues 207-218. Lin does not disclose a binding epitope which includes the binding epitope identified by the Applicants. Furthermore, the functional effect which is mediated by the beta 1 antibody disclosed in Lin is functionally distinct from that achieved by the Applicants' beta 1 integrin modulation.

Further, the Applicants respectfully submit that angiogenesis and tissue repair are not synonymous. Angiogenesis is accompanied by cell proliferation, whereas the Applicants modulate tissue repair by binding a modulator compound to beta 1 integrin at an epitope comprising amino acid residues 82-87. This binding, in turn, mediates a number of effects, such as the reduction in apoptosis, with the focus of this being epithelial-mesenchymal populations. The beta 1 integrin modulation observed in this application did not increase cell proliferation.

With regard to the comments in the rejection that "While the prior art teachings may be silent as to the peptide/antibody "modulates the MMP balance", "modulates apoptosis" "wherein the modulation of apoptotic activity has a resultant modulation in the MMP balance" per se; the method, the product used in the reference method are the same as the claimed method. Therefore, these claimed limitations are considered inherent properties of the referenced compounds." The Applicants respectfully disagree. It is incorrect to extrapolate that just because 2 groups of compounds bind to the same target ligand that they mediate the same end effect. This is particularly the case when the compounds of the prior art and the Applicants' compounds are compared, as they in fact bind to different epitopes of beta-1 integrin. In the specific case of antibodies binding to different target epitopes on the same ligand, it cannot be simply concluded

that two antibodies will mediate the same downstream effect on a ligand purely because they have binding specificity for it. Those skilled in the art are well versed in the principles of antibody binding and are fully cognisant of the fact that antibodies binding to different epitopes on the same ligand, can not be assumed to mediate identical effector functions. Hence, the Applicants disagree with the assertion that the beta 1 integrin binding compounds of Lin would mediate the effects disclosed in the solicited claims simply because the P4C10 antibody binds to beta 1 integrin. The Applicants therefore respectfully submit that Lin does not anticipate the solicited claims.

Claims 1-4 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 6,251,419. '419 is submitted to disclose the use of a membrane system for the controlled tissue regeneration of the periodontium, comprising a resorbable polymer membrane comprising an antibody which binds to a beta 1 integrin subunit.

Column 1, line 52 through to column 2, line 4 of '419 teaches that "All molecules which compensate the effect of adhesion molecules are suitable as anti-adhesion molecules. Adhesion molecules are generally understood to mean molecules which play an essential part in the cell-to-cell communication, in particular they are understood to mean the integrins which were also identified in the periodontium. For compensating the effect exerted by the adhesion molecules, competitive proteins and peptides, respectively, are suited for this purpose (what is called disintegrins or disintegrin-like proteins and peptides, respectively) as well as antibodies directed against the adhesion molecules, which can be purchased. Examples are monoclonal mouse antibodies against ... integrin subunit beta-1 (clone P4c10; Biomol, Hamburg)."

'419 therefore teaches the use of the P4C10 clone, as also used in the cited art of Lin and Leu discussed hereinbefore. Hence, as mentioned, the P4C10 antibody has binding specificity

for amino acid residues 207-218 in the beta A domain of beta 1 integrin. This epitope is different and distinct from the epitope comprising residues 82-87 which is present in the hybrid domain of beta 1 integrin which is recited in amended Claim 1 and which is bound by the modulator compounds. Furthermore, modulation of beta 1 integrin at the epitope comprising residues 82-87 of the hybrid domain does not result in an inhibition of adhesion, as occurs in '419. Hence, not only does '419 teach of a beta 1 integrin modulator which binds to an epitope which is remote from that bound by the modulator compounds, but '419 teaches of a different function effect once the beta 1 integrin has been bound by the P4C10 antibody.

The Applicants therefore respectfully submit that '419 does not anticipate Claims 1 – 4 and 15. Withdrawal of the rejection is respectfully requested.

In light of the foregoing, the Applicants respectfully submit that the entire application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

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